UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
[illegible]
Washington [illegible]
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/543,771	04/05/2000	John P. Caraffi	032796-014	6685

21839 7590 03/12/2003

BURNS DOANE SWECKER & MATHIS L. L. P
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
2636	7

DATE MAILED: 03/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/543,771	CARULLI ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 December 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,14-19 and 26-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1 and 34* is/are allowed.

6)☒ Claim(s) *14-19,26-31,35 and 36* is/are rejected.

7)☒ Claim(s) *32 and 33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.*

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)*
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15,10*.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/24/02 has been entered.

Claims 2-13, 24 and 25 are canceled.

Claims 30-36 are newly filed.

Claims 1, 14-19, 26-36 are pending and are examined in this office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. The references cited herein are of record in a prior Office action.

► *Applicants are advised to follow Amendment Practice under revised 37 CFR §1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm). Each amendment document that includes a change to an existing claim, or submission of a new claim,* ***must include a complete listing of all claims*** *in the application. After each claim number, the status must be indicated in a parenthetical expression, and the text of each claim under examination (with markings to show current changes) must be presented. The listing will serve to replace all prior versions of the claims in the application.*

Information Disclosure Statement

In response to applicant's request, please see the attached copy of 1449A/PTO dated 04/25/02 (Paper #15) and 06/08/01 (Paper #10).

Claim Rejections - 35 USC § 112

1. Claims 14-19 and 26-29 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention for the same reasons of record as set forth in the earlier official action mailed on the 11/12/02.

2. In addition, claims 30-31 and 35-36 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated amino acid sequence of SEQ ID NO:4 or extracellular domain of the amino acid sequence of SEQ ID NO:4 (23-1385), does not reasonably provide enablement for any biologically active bone modulating fragments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention **commensurate in scope** with these claims.

Rejection of claims 14-19, 26-31 and 35-36 regarding enablement issues are discussed below in response to applicant's argument filed on 10/31/02.

Response to argument

The applicant argues that the specification fully enables the claimed methods of altering bone development and treatment. The applicant argues that since HBM carriers are not susceptible to a disease characterized by reduced bone density, such individuals are equivalent to individual being treated with HBM protein (response, page 5 para.3). The applicant argues that

the specification provides Northern blot testing and PCR analysis to demonstrate that this protein is expressed in variety of bone tissues (response, page 6 para.1). The applicant argues that Kato and Boyden teach that LPR5 regulates *wnt* signal transduction therefore the specification is fully enables for the use of HBM protein to alter bone development (response, page 7). The applicant persists that similarity between LDRP5 and HBM dose not negate the evidence provided in the specification that individuals expressing HBM protein are protected from diseases such as osteoporosis. The applicant argues that office provide no evidence that why HBM' close similarity to LPR5 would eliminate the role of HBM in bone development (response, page 8).

However, this is found NOT persuasive because applicant's argument alone cannot take place of evidence lacking in the record (see In re Scarbrough 182 USPQ, (CCPA) 1979). The scope of invention as claimed encompasses a method of a of altering bone development in host comprising administering the i) amino acid of SEQ ID NO:4, ii) the extracellular domain of the amino acid of SEQ ID NO:4 and iii) intracellular domain of the amino acid of SEQ ID NO:4. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The instant specification fails to provide a single working example that establishes that the administration administering the i) SEQ ID NO:4, ii) the extracellular domain of SEQ ID NO:4, or iii) intracellular domain SEQ ID NO:4, leads to bone development and/or the treatment of osteoporosis in any and all vertebrates. The specification even fails to provide any guidance regarding the role of amino acid of SEQ ID NO:4 in the bone development and/or osteoporosis. Mere identification of HBM-expression does not provide any evidence that the exogenous administration of HBM-protein or a fragment

thereof would alters the bone development, since applicant fails to disclose how HBM or Zmax regulates the bone development.

The state of the art at the time of filing teaches that the development of bones is not only polygenic but is also affected by various growth factors, hormones, nutrient uptake and pathogens. The strength and integrity of bones depends on maintaining a delicate balance between bone re-absorption by osteoclasts and bone formation by osteoblasts. With aging or as a result of disease, this delicate balancing act becomes tipped in favor of osteoclasts so that bone resorption exceeds bone formation, rendering bones brittle and prone to fracture. (Radan et al, Science 289:1508-1514, 2000, abstract). Furthermore, the osteoporosis is a multifactorial disorder characterized by low bone mass and micro architectural deterioration of bone structure. The incidence of osteoporosis is higher in women than in men and increases sharply after 50 yrs of age. Recent studies reveled that genetic factors plays an important role in the pathogenesis of osteoporosis and the segregation analysis reveled that bone mineral density is under polygenic control (Kundu et al, Peptides 20:523-537, 1999. page 523, col.1-2). The most common cause of osteoporosis in women is the decrease in estrogen that accompanies menopause. Estrogen loss is associated with elevated bone resorption caused by a rise in osteoclast number, which is driven by increases in the cytokines that regulate osteoclast generation (RANK-ligand, TNF-a, IL-1, IL-6, IL-11, M-CSF and prostaglandin E). Production of all of these cytokines is either directly or indirectly suppressed or regulated by estrogen (Rodan, page 1509, col.1, para. 3). Several hormones also regulate the bone mineralization and demineralization, primarily by parathyroid hormone (PTH). The higher concentration of PTH inhibits the bone formation whereas the low serum concentration increases the bone mass (Kundu et al page 524, col. 2, sec. 4.1; Ziegler et al,

Steroids 63:344-348, 1998, page 345, fig-1). In addition, bone formation is also affected by nutrient uptake. The reduced caloric intake is associated with reduced calcium intake which results in decrease in bone mass over time (Bollag et al, Endocrinology, 141(3)1228-35, 2000, page 1234, col.1 para.2). Considering the multifactorial nature of bone development the alteration of bone development is considered highly unpredictable especially in view of instant disclosure, since the specification fails to disclose the role of amino acid of SEQ ID NO:4 in bone development and/or the treatment of osteoporosis via any and all means. The specification fails to disclose that the administration of HBM protein leads to any change in osteoblast (increase) or osteoclast (decrease) activity that results in bone formation. Furthermore, considering the applicant's disclosure it is even unclear that HBM-protein modulates any hormone like PTH that regulates bone development. Similarly, the specification fails to disclose that HBM affects estrogen levels and/or its activity, or cytokines that affects osteoclast number or their activity. Thus considering the instant disclosure it is unclear how one skill in the art would identify SEQ ID NO:4 or a fragment thereof that would have any bone modulating activity, since the specification fails to disclose a single assay that one skill in the art would use to evaluate the bone modulating activity of SEQ ID NO:4 specifically.

In addition, the official sequence search reveled that the amino acid sequences of SEQ ID NO:4 matches 99.6% to the amino acid sequence of a Low Density Lipoprotein Receptor Related Protein (LRP5) expressed in hepatocytes and adrenal cortex and is know to play a key role in the hepatic clearance of cholesterol carrying LDL (Kim et al, J Biochem. (Tokyo) 124:1072-1076, 1998, page 1072, col.1). Considering the high amino acid sequence homology (99.6%) one skill in the art would conclude that the amino acid sequence of SEQ ID NO:4 falls

in the realm of LDL-receptor-related-protein family that would regulate hepatic clearance of cholesterol carrying LDL. The administration of HBM or extracellular domain thereof would be non-productive, since it would only complete with a natural ligand for HBM receptor protein (*which is LDL*). The specification fails to disclose a single natural ligand (*other than LDL*) for the extracellular domain of HBM-receptor protein, blocking of which regulates the bone formation by modulating endogenous Zmax1 function. At best the only know ligand for the SEQ ID NO:4 would be LDL (see Kim et al) and it is unclear how one skill in the art would regulate bone development and or osteoporosis by blocking LDL activity. Furthermore, the applicant fails to disclose how the administration of HBM-intercellular domain would modify the interacellular signal transduction of bone cells, which would takes over the endogenous Zmax1 function. Even though the applicant asserts that HBM is involved in wnt signal transduction, the specification fails to provide any evidence whether the high bone mass (HBM) phenotype is the result of the loss of Zmax1 protein activity or is the result of altered Zmax1 protein function due to the HBM mutation. The polypeptide (SEQ ID NO:4) as claimed appears to be a receptor comprising extracelluar and interacelluar domains. It is unclear how one skill in the art would purify the receptor (as claimed) and soluble but active state, which upon administration to a subject would not loose its specific activity due to in vivo degradation. Furthermore it is unclear how one skill in the art would use a fragment of SEQ ID NO:4 to modulate a signal transduction mechanism, since the specification even fails disclose the role of HBM/Zmax1 in any signal transduction cascade, that leads to bone development. Furthermore, the specification fails to provide any guidance regarding the role of HBM/Zmax1in signal transduction in development of germ line cells, therefore it is unclear how an administration of HBM-protein would modulate

the bone development in embryonic development and/or leads to the alteration of bone development in a mature animal. It is even unclear what would be the molecular target of HBM-protein or fragment thereof on a cellular basis. For example, it is unclear whether the HBM polypeptide affects osteoblast/osteoclast activity or modulates a hormone like PTH, which regulates bone development.

Furthermore, it is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson , 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

In instant case the use of an uncharacterized protein or fragments thereof to induce bone development and/or treat osteoporosis is not considered routine in the art and without sufficient guidance to a specific mechanism by which the HBM affects the bone development the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue

amount of experimentation to exercise the invention as claimed. The amount of experimentation required would include administration of the amino acid sequence of SEQ ID NO:4, extracellular or intercellular domain of SEQ ID NO:4 into patients suffering from any and all bone defects (Osteoporosis, Paget disease, Bone cancer, Inflammatory bone disease etc) and the evaluation of bone development. Thus, the burden shifts to applicant to establish that the invention as claimed can be used to treat any bone defects because the Office has clearly provided sufficient evidence and sound scientific reasoning to rebut applicant's assertion

3. Claims 30-31 and 35-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The scope of invention as claimed encompasses any and all biologically active bone modulating fragments of the amino acid sequences of SEQ ID NO:4 or a biologically active bone modulating fragment of the extracellular domain of amino acid sequences of SEQ ID NO:4. At best the specification disclosed the amino acid of SEQ ID NO:4 but fails to disclose a fragment of SEQ ID NO:4 or an extercellular domain of SEQ ID NO:4 has any bone modulating activity explicitly or implicitly as putatively considered by the applicant.

The state of the art at the time of filing teaches that the development of bones is not only polygenic but is also affected by various growth factors, hormones, nutrient uptake and pathogens *(supra)*. Considering the multifactorial nature of bone development the alteration of

bone development is considered highly unpredictable especially in view of instant disclosure, wherein the instant specification fails to disclose the role of amino acid of SEQ ID NO:4 in bone development via any and all means. Thus considering the instant disclosure it is unclear how one skill in the art would identify a fragment SEQ ID NO:4 that would have any bone modulating activity, since the specification fails to disclose a single assay that one skill in the art would use to evaluate the bone modulating activity of SEQ ID NO:4 or a fragment thereof. The possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).* In the instant case the claimed fragment has been defined only by a statement of bone modulating function, which conveyed no distinguishing information about the identity of the claimed DNA sequence, such as its relevant structural or physical characteristics. According

to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

Claim Objections

4. Claims 32-33 and 35-36 are objected to because of the following informalities: Claims 32 and 35 recite a claim limitation "extracellular domain of amino acid of SEQ ID NO:4" without identifying the amino acid sequence comprising the extracellular domain. Identification of amino acid 23-1385 of SEQ ID NO:4 that comprises an extracellular domain has been suggested. Appropriate correction is required.

5. Claim 28 is objected to because of the following informalities: Instant claim recites " an isolated amino acid of SEQ ID NO:1", however, SEQ ID NO:1 is a nucleic acid sequence. Appropriate correction is required.

Conclusion

Claims 1 and 34 are allowed.
Claims 32-33 are objected
Claims 14-19 and 26-31 and 35-36 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be

reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal